



AU9190873

BEST AVAILABLE COPY

(12) PATENT ABRIDGMENT (11) Document No. AU-B-90873/91
(19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 658854

- (54) Title
AEROSOL FORMULATION COMPRISING BECLOMETHASONE 17,21 DIPROPIONATE
- International Patent Classification(s)
(51)⁵ A61K 009/12 A61K 031/57
- (21) Application No. : 90873/91 (22) Application Date : 09.10.91
- (87) PCT Publication Number : WO92/06675
- (30) Priority Data
- | | | |
|-------------|-----------|-----------------------------|
| (31) Number | (32) Date | (33) Country |
| 599694 | 18.10.90 | US UNITED STATES OF AMERICA |
- (43) Publication Date : 20.05.92
- (44) Publication Date of Accepted Application : 04.05.95
- (71) Applicant(s)
MINNESOTA MINING AND MANUFACTURING COMPANY
- (72) Inventor(s)
ROBERT K SCHULTZ; DAVID W SCHULTZ
- (74) Attorney or Agent
PHILLIPS ORMONDE & FITZPATRICK, 367 Collins Street, MELBOURNE VIC 3000
- (56) Prior Art Documents
AU 72113/91 A61K 009/12
AU 72116/91 A61K 009/12
- (57) Claim

1. An aerosol formulation ~~comprising~~^{including} a therapeutically effective amount of beclomethasone 17,21 dipropionate, a propellant ~~comprising~~^{including} a hydrofluorocarbon selected from the group consisting of 1,1,1,2-tetrafluoroethane, 1,1,1,2,3,3,3-heptafluoropropane, and a mixture thereof, and ethanol in an amount effective to solubilize the beclomethasone 17,21 dipropionate in the propellant, the formulation being further characterized in that substantially all of the beclomethasone 17,21 dipropionate is dissolved in the formulation, and that the formulation contains no more than 0.0005% by weight of any surfactant.

14. A method of preparing a solution aerosol formulation according to claim 1 including the step of combining a therapeutically effective amount of beclomethasone 17, 21 dipropionate, a propellant selected from the group consisting of 1,1,1,2-tetrafluoroethane, 1,1,1,2,3,3,3-heptafluoro- propane, and a mixture thereof, and an amount of ethanol effective to solubilize the beclomethasone 17,21 dipropionate in the propellant.

OPI DATE 20/05/92

APPLN. ID

90873 / 91



INTERN. A0JP DATE 25/06/92

PCT NUMBER PCT/US91/07574

TREATY (PCT)

(51) International Patent Classification 5 : A61K 9/12	A1	(11) International Publication Number: WO 92/06675 (43) International Publication Date: 30 April 1992 (30.04.92)
(21) International Application Number: PCT/US91/07574 (22) International Filing Date: 9 October 1991 (09.10.91) (30) Priority data: 599,694 18 October 1990 (18.10.90) US (71) Applicant: MINNESOTA MINING AND MANUFACTURING COMPANY [US/US]; 3M Center, Post Office Box 33427, Saint Paul, MN 55133-3427 (US). (72) Inventors: SCHULTZ, Robert, K. ; SCHULTZ, David, W. ; Post Office Box 33427, Saint Paul, MN 55133-3427 (US). (74) Agents: REEDICH, Douglas, E. et al.; Intellectual Property Counsel, Minnesota Mining and Manufacturing Company, Post Office Box 33427, Saint Paul, MN 55133-3427 (US).		(81) Designated States: AT (European patent), AU, BE (European patent), CA, CH (European patent), DE (European patent), DK (European patent), ES (European patent), FR (European patent), GB (European patent), GR (European patent), IT (European patent), JP, LU (European patent), NL (European patent), SE (European patent). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i> 658854
(54) Title: AEROSOL FORMULATION COMPRISING BECLOMETHASONE 17,21 DIPROPIONATE (57) Abstract Pharmaceutical solution aerosol formulations comprising beclomethasone 17,21 dipropionate, ethanol, and a propellant selected from the group consisting of 1,1,1,2-tetrafluoroethane, 1,1,1,2,3,3,3-heptafluoropropane, and a mixture thereof.		

Aerosol formulation comprising beclomethasone 17,21 dipropionate.

5 TECHNICAL FIELD OF THE INVENTION

 This invention pertains to solution aerosol formulations suitable for use in administering drugs. In another aspect this invention pertains to formulations comprising beclomethasone 17,21 dipropionate.

10

BACKGROUND OF THE INVENTION

 Pharmaceutical suspension aerosol formulations currently use a mixture of liquid chlorofluorocarbons as the propellant. Fluorotrichloromethane,
15 dichlorodifluoromethane and dichlorotetrafluoroethane are the most commonly used propellants in aerosol formulations for administration by inhalation.

 Chlorofluorocarbons have been implicated in the destruction of the ozone layer and their production is
20 being phased out. Hydrofluorocarbon 134a (HFC-134a, 1,1,1,2-tetrafluoroethane) and hydrofluorocarbon 227 (HFC-227, 1,1,1,2,3,3,3-heptafluoropropane) are viewed as being less destructive to ozone than many chlorofluorocarbon propellants; furthermore, they have low toxicity and vapor
25 pressure suitable for use in aerosols.

 Beclomethasone 17,21 dipropionate is commercially available as an aerosol product comprising a suspension of a chlorofluorohydrocarbon solvate of beclomethasone 17,21 dipropionate in
30 chlorofluorohydrocarbon propellants. Preparation of the solvate requires several processing steps and is required in order to obtain a stable aerosol formulation, i.e., one in which the micronized particles of active ingredient remain in the desired respirable particle size range. A
35 solution formulation of beclomethasone 17,21 dipropionate could simplify formulation manufacture and increase the respirable fraction (i.e., the percentage of active ingredient able to reach the airways of the lung where the pharmaceutical effect is exerted).

U.S. Pat. No. 2,868,691 discloses a self-propelling pharmaceutical aerosol formulation comprising i) a medicament; ii) a propellant represented generally by the formula $C_mH_nCl_yF_z$, wherein m is an integer less than 3, n is an integer or zero, y is an integer or zero, and z is an integer, such that $n + y + z = 2m + 2$; and iii) a cosolvent which assists in the dissolution of the medicament in the propellant. Ethanol is an example of a cosolvent disclosed in this patent. The above formula representing the propellant component generically embraces HFC-134a. This patent does not, however, disclose beclomethasone 17,21 dipropionate or suggest how stable solution aerosol formulations (i.e., formulations that are chemically stable and exhibit desirable respirable fraction) containing any propellant and beclomethasone 17,21 dipropionate can be prepared.

European Patent Publication No. 0372777 discloses a self-propelling aerosol formulation which may be free from CFC's which comprises a medicament, 1,1,1,2-tetrafluoroethane, a surface active agent and at least one compound having a higher polarity than 1,1,1,2-tetrafluoroethane. Examples 10 to 12 disclose solution formulations comprising beclomethasone 17,21 dipropionate (0.005g), surface active agent (0.006g), (sorbitan trioleate, oleic acid and lecithin in Examples 10 to 12 respectively), ethanol (1.350g) and 1,1,1,2-tetrafluoroethane (4.040g).



SUMMARY OF THE INVENTION

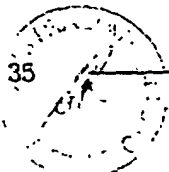
The present invention provides an aerosol formulation comprising a therapeutically effective amount of beclomethasone 17,21 dipropionate, a propellant
5 comprising a hydrofluorocarbon selected from the group consisting of 1,1,1,2-tetrafluoroethane, 1,1,1,2,3,3,3-heptafluoropropane, and a mixture thereof, and ethanol in an amount effective to solubilize the beclomethasone 17,21 dipropionate in the propellant, the formulation being
10 further characterized in that substantially all of the beclomethasone 17,21 dipropionate is dissolved in the formulation, and the formulation is substantially free of any surfactant.

Certain of the preferred formulations of the
15 invention exhibit very desirable chemical stability and provide respirable fractions significantly greater than commercially available beclomethasone 17,21 dipropionate products. Moreover, the formulations of the invention are convenient to manufacture since no solvate of the active
20 ingredient need be prepared.

The pharmaceutical solution aerosol formulations of the invention are suitable for pulmonary, buccal, or nasal administration.

25

30



SUBSTITUTE SHEET

DETAILED DESCRIPTION OF THE INVENTION

All weight percentages recited herein are based on the total weight of the formulation unless otherwise indicated.

5 The medicament beclomethasone 17,21 dipropionate is generally present in a formulation of the invention in a therapeutically effective amount, i.e., an amount such that one or more metered volumes of the formulation contains an amount of drug effective to exert the intended therapeutic
10 action. Preferably the medicament will constitute about 0.02 to about 0.6 percent by weight, more preferably about 0.05 to about 0.5 percent by weight of the total weight of the formulation.

 Ethanol is generally present in an amount
15 effective to solubilize the beclomethasone 17,21 dipropionate in the propellant. Preferably, ethanol constitutes about 1 to about 20 percent by weight of the total weight of the aerosol formulation. More preferably, ethanol constitutes about 2 to about 12 percent by weight
20 and even more preferably about 2 to about 10 percent by weight of the aerosol formulation. Most preferably, ethanol will be present in an amount sufficient to dissolve substantially all of the medicament present in the formulation and to maintain the medicament dissolved over
25 the time period and conditions experienced by commercial aerosol products, but not substantially in excess of said amount. Particularly desirable formulations of the invention, while not containing amounts of ethanol substantially in excess of that required (during
30 manufacture of the formulation) to dissolve the amount of active ingredient employed, may be subjected to a temperature of -20°C. without precipitation of the active ingredient.

 The hydrofluorocarbon propellant can be HFC-
35 134a, HFC-227, or a mixture thereof. The propellant preferably constitutes from about 80 to about 99 percent by weight, preferably from about 88 to about 98 percent by weight, and more preferably about 90 to about 98 percent by weight of the total weight of the aerosol formulation. The
40 hydrofluorocarbon propellant is preferably the only

propellant present in the formulations of the invention. However, one or more other propellants (e.g., 1-chloro-1,1-difluoroethane) can also be present.

The formulations of the invention are substantially free of any surfactant. By "substantially free" as used in the instant specification and claims is meant that the formulations contain no more than 0.0005 percent by weight of a surfactant based on the total weight of the formulation. Preferred formulations contain no surfactant. Presence of a significant amount of a surfactant is believed to be undesirable in the case of solution formulations of beclomethasone 17,21 dipropionate because surfactants such as oleic acid and lecithin seem to promote chemical degradation of the active ingredient when the latter is dissolved in the mixture of HFC-134a and ethanol.

Preferred formulations according to the invention consist essentially of beclomethasone 17,21 dipropionate in an amount of about 0.05 to about 0.35 percent by weight based on the weight of the total formulation, ethanol in an amount of about 2 to about 8 percent by weight based on the total weight of the formulation, and 1,1,1,2-tetrafluoroethane.

The solution formulations of the invention can be prepared by dissolving the desired amount of beclomethasone 17,21 dipropionate in the desired amount of anhydrous ethanol accompanied by stirring or sonication. The aerosol vial may then be filled using conventional cold-fill or pressure-fill methods.

The following examples are provided to illustrate the invention but should not be construed as limiting the invention.

Examples 1 - 7

Formulations containing the following ingredients (TABLE I) in the indicated amounts were prepared with the percentages being expressed in parts by weight based upon the total weight of the particular formulation. The active ingredient employed in preparing the formulations of Examples 2, 3, and 5 - 7 was

beclomethasone dipropionate, USP while that employed in preparing the formulations of Examples 1 and 4 was a conventional trichloromonofluoromethane solvate of beclomethasone dipropionate. The formulations of Examples 1, 4, 5 and 6 were prepared by i) dissolving the active ingredient in the ethanol; ii) metering the solution obtained above into an aluminum vial and crimping a continuous valve onto the vial; iii) pressure-filling the vial with 1,1,1,2-tetrafluoroethane; iv) chilling the vial to -60°C.; and v) replacing the continuous valve with a 50 microliter valve which is available under the trade designation "W303-98" from 3M. The formulations of Examples 2, 3 and 7 were prepared by i) dissolving the active ingredient in the ethanol; ii) metering the solution obtained above into an aluminum vial and crimping a 50 microliter pressure-fill valve which is available under the trade designation Spraymiser™ M3652 from 3M onto the vial; and iii) pressure-filling the vial with 1,1,1,2-tetrafluoroethane.

The actuator employed in the case of all the formulations was a solution actuator available under the trade designation "M3756" from 3M. The elastomer employed in the valves in the case of all formulations was that available under the trade designation "DB-218" from American Gasket and Rubber Co. (Chicago, IL.)

TABLE I

<u>Ingredient</u>	<u>Example</u>						
	1	2	3	4	5	6	7
Beclomethasone 17,21 Dipropionate	0.1%	0.1%	0.25%	0.3%	0.4%	0.44%	0.5%
Ethanol (anhydrous)	3%	5%	10%	5%	10%	10%	15%
1,1,1,2-Tetra- fluoroethane	96.9%	94.9%	89.75%	94.7%	89.6%	89.56%	84.5%

The chemical stability of the formulation of Example 4 was determined in respect to recovery of the active ingredient over time when the formulation was stored at 40°C. TABLE II contains the data.

5

TABLE II

Storage Time (Weeks)	0	2	4	7	12
	% Recovery	% Recovery	% Recovery	% Recovery	% Recovery
10	101.4, 98.7	101.9, 101.6	100.8, 99.6	99.3, 95.5	100.6 102.6

15

The formulation of Example 1 did not exhibit precipitation of the active ingredient on freezing to -60°C.

The respirable fraction provided by the formulations of Examples 1 - 7 was determined using an Anderson MK II Cascade Impactor with the average respirable fraction obtained from each being in excess of 40%. In the case of the formulations of Examples 1 and 4, the respirable fraction was about 76% and about 70%, respectively.

From the above data, it is believed that the optimum amount of active ingredient for low and high strength products would be about 0.08 and 0.34 percent by

weight, respectively, based on the total weight of the formulations.

Example 8

5 A mixture containing 1.67 g of beclomethasone
17,21 dipropionate and 160g of cold (-65°C) ethanol was
homogenized using a Virtis 45 homogenizer. The resulting
suspension was placed in a one gallon stainless steel
filling vessel equipped with a stir bar. A 1839 g portion
10 of cold (-65°C) 1,1,1,2-tetrafluoroethane was added to the
filling vessel. After about 5 minutes of stirring, a
solution was obtained. The resulting formulation contained
0.08 percent by weight of beclomethasone 17,21
dipropionate, 8.0 percent by weight of ethanol and 91.92
15 percent by weight of 1,1,1,2-tetrafluoroethane. The
formulation was cold filled into aerosol vials and then 50
µL cold fill valves were crimped onto the vials.

Example 9

20 Using the general method of Example 8, a
formulation containing 0.34 percent by weight of
beclomethasone 17,21 dipropionate, 8.0 percent by weight of
ethanol and 91.66 percent by weight of 1,1,1,2-
tetrafluoroethane was prepared. The formulation was cold
25 filled as a suspension into aerosol vials which were then
equipped with 50 µL cold fill valves. The formulation
changed from a suspension to a solution as the vials warmed
to room temperature.

Example 10

30 A formulation containing 0.3 percent by weight
of beclomethasone 17,21 dipropionate, 10 percent by weight
of ethanol and 89.7 percent by weight of 1,1,1,2,3,3,3-
heptafluoropropane was prepared by i) weighing a 30 mg
35 portion of beclomethasone 17,21 dipropionate into an
aerosol vial ii) crimping a continuous valve onto the vial
and iii) pressure filling with a solution containing 10
percent ethanol in 1,1,1,2,3,3,3-heptafluoropropane.

~~WHAT IS CLAIMED IS:~~
The Claims defining the invention are, as follows:

1. An aerosol formulation ^{including} ~~comprising~~ a therapeutically effective amount of beclomethasone 17,21 dipropionate, a propellant, ^{including} ~~comprising~~ a hydrofluorocarbon selected from the group consisting of 1,1,1,2-tetrafluoroethane, 1,1,1,2,3,3,3-heptafluoropropane, and a mixture thereof, and ethanol in an amount effective to solubilize the beclomethasone 17,21 dipropionate in the propellant, the formulation being further characterized in that substantially all of the beclomethasone 17,21 dipropionate is dissolved in the formulation, and that the formulation contains no more than 0.0005% by weight of any surfactant.
2. A solution aerosol formulation according to Claim 1, ^{including} ~~comprising~~ between 0.02 and about 0.6 percent by weight beclomethasone 17,21 dipropionate, between about 1 and about 20 percent by weight ethanol, and between about 80 and about 99 percent by weight of said propellant.
3. A solution aerosol formulation according to Claim 1 wherein said beclomethasone 17,21 dipropionate is present in an amount of about 0.05 to about 0.5 percent by weight.
4. A solution aerosol formulation according to Claim 1 wherein said ethanol is present in an amount of about 2 to about 12 percent by weight.
5. A solution aerosol formulation according to Claim 1 wherein said ethanol is present in an amount of about 2 to 10 percent by weight.
6. A solution aerosol formulation according to Claim 1 wherein said propellant is present in an amount of about 88 to about 98 percent by weight.



SUBSTITUTE SHEET

7. A solution aerosol formulation according to Claim 1 comprising 1,1,1,2-tetrafluoroethane as substantially the only propellant.

5 8. A solution aerosol formulation according to Claim 1 comprising 1,1,1,2,3,3,3-heptafluoropropane as substantially the only propellant.

10 9. A solution aerosol formulation according to Claim 1 ^{including} ~~comprising~~ beclomethasone 17,21 dipropionate in an amount of about 0.05 to about 0.5 percent by weight, ethanol in an amount of about 2 to about 12 percent by weight and said propellant in an amount of about 88 to about 98 percent by weight.

15 10. A solution aerosol formulation according to Claim 1 ^{including} ~~comprising~~ beclomethasone 17, 21 dipropionate in an amount of about 0.05 to about 0.45 percent by weight, ethanol in an amount of about 2 to about 10 percent by weight and said propellant in an amount of about 90 to about 98 percent by weight.

25 11. A solution aerosol formulation according to Claim 1, consisting essentially of beclomethasone 17,21 dipropionate in an amount of about 0.05 to about 0.35 percent by weight, ethanol in an amount of about 2 to about 8 percent by weight, and 1,1,1,2-tetrafluoroethane.

30 12. A solution aerosol formulation according to Claim 1, wherein the amount of ethanol present is not substantially in excess of the amount required to dissolve substantially all of the beclomethasone 17,21 dipropionate, but is sufficient to permit said formulation to be subjected to a temperature of -20°C. without significant precipitation of said beclomethasone 17, 21 dipropionate.

35 13. A method of treating bronchial asthma in a mammal ^{including} ~~comprising~~ administering to said mammal an amount of



a formulation according to Claim 1 sufficient to treat the asthmatic condition.

5

14. A method of preparing a solution aerosol formulation according to claim 1 including the step of combining a therapeutically effective amount of beclomethasone 17, 21 depropionate, a propellant selected from the group
10 consisting of 1,1,1,2-tetrafluoroethane, 1,1,1,2,3,3,3-heptafluoro- propane, and a mixture thereof, and an amount of ethanol effective to solubilize the beclomethasone 17,21 dipropionate in the propellant.

15 15. An aerosol formulation substantially as hereinbefore described with reference to any one of the Examples.

16. A method of preparing a solution aerosol formulation substantially as hereinbefore described with reference to
20 any one of the Examples.

DATED: 17 FEBRUARY, 1995

25

PHILLIPS ORMONDE & FITZPATRICK"

Attorneys for:

MINNESOTA MINING AND MANUFACTURING COMPANY

30

David B Fitzpatrick

35



INTERNATIONAL SEARCH REPORT

International Application No PCT/US 91/07574

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all) ⁶ According to International Patent Classification (IPC) or to both National Classification and IPC IPC5: A 61 K 9/12														
II. FIELDS SEARCHED <div style="text-align: center; border-top: 1px solid black; border-bottom: 1px solid black;">Minimum Documentation Searched⁷</div> <table style="width: 100%; border-collapse: collapse;"> <tr> <th style="width: 20%; border: 1px solid black; padding: 5px;">Classification System</th> <th style="border: 1px solid black; padding: 5px;">Classification Symbols</th> </tr> <tr> <td style="border: 1px solid black; padding: 10px; vertical-align: top;">IPC5</td> <td style="border: 1px solid black; padding: 10px; vertical-align: top;">A 61 K</td> </tr> </table> <div style="text-align: center; border-top: 1px solid black; border-bottom: 1px solid black;">Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in Fields Searched⁸</div>			Classification System	Classification Symbols	IPC5	A 61 K								
Classification System	Classification Symbols													
IPC5	A 61 K													
III. DOCUMENTS CONSIDERED TO BE RELEVANT⁹ <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th style="width: 10%; padding: 5px;">Category¹⁰</th> <th style="width: 60%; padding: 5px;">Citation of Document,¹¹ with indication, where appropriate, of the relevant passages¹²</th> <th style="width: 30%; padding: 5px;">Relevant to Claim No.¹³</th> </tr> </thead> <tbody> <tr> <td style="text-align: center; vertical-align: top; padding: 5px;">P,X</td> <td style="padding: 5px;">WO, A1, 9111173 (FISONS PLC) 8 August 1991, see the whole document --</td> <td style="text-align: center; vertical-align: top; padding: 5px;">1-14</td> </tr> <tr> <td style="text-align: center; vertical-align: top; padding: 5px;">P,X</td> <td style="padding: 5px;">WO, A1, 9111495 (BOEHRINGER INGELHEIM INTERNATIONAL) 8 August 1991, see the whole document --</td> <td style="text-align: center; vertical-align: top; padding: 5px;">1-14</td> </tr> <tr> <td style="text-align: center; vertical-align: top; padding: 5px;">A</td> <td style="padding: 5px;">WO, A1, 8603750 (RIKER LABORATORIES, INC.) 3 July 1986, see the whole document -----</td> <td style="text-align: center; vertical-align: top; padding: 5px;">1-14</td> </tr> </tbody> </table>			Category ¹⁰	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³	P,X	WO, A1, 9111173 (FISONS PLC) 8 August 1991, see the whole document --	1-14	P,X	WO, A1, 9111495 (BOEHRINGER INGELHEIM INTERNATIONAL) 8 August 1991, see the whole document --	1-14	A	WO, A1, 8603750 (RIKER LABORATORIES, INC.) 3 July 1986, see the whole document -----	1-14
Category ¹⁰	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³												
P,X	WO, A1, 9111173 (FISONS PLC) 8 August 1991, see the whole document --	1-14												
P,X	WO, A1, 9111495 (BOEHRINGER INGELHEIM INTERNATIONAL) 8 August 1991, see the whole document --	1-14												
A	WO, A1, 8603750 (RIKER LABORATORIES, INC.) 3 July 1986, see the whole document -----	1-14												
<div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p>¹⁰ * Special categories of cited documents:</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 45%;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance, the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance, the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art</p> <p>"A" document member of the same patent family</p> </div> </div>														
IV. CERTIFICATION <table style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 50%; border: 1px solid black; padding: 5px;"> Date of the Actual Completion of the International Search 9th March 1992 </td> <td style="width: 50%; border: 1px solid black; padding: 5px;"> Date of Mailing of this International Search Report 25.03.92 </td> </tr> <tr> <td style="border: 1px solid black; padding: 5px;"> International Searching Authority EUROPEAN PATENT OFFICE </td> <td style="border: 1px solid black; padding: 5px;"> Signature of Authorized Officer Mme. M. van der Drift </td> </tr> </table>			Date of the Actual Completion of the International Search 9th March 1992	Date of Mailing of this International Search Report 25.03.92	International Searching Authority EUROPEAN PATENT OFFICE	Signature of Authorized Officer Mme. M. van der Drift								
Date of the Actual Completion of the International Search 9th March 1992	Date of Mailing of this International Search Report 25.03.92													
International Searching Authority EUROPEAN PATENT OFFICE	Signature of Authorized Officer Mme. M. van der Drift													

**ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO.PCT/US 91/07574**

SA 54160

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 01/02/92. The European Patent office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A1- 9111173	08/08/91	NONE		
WO-A1- 9111495	08/08/91	AU-D-	7211391	21/08/91
		DE-A-	4003272	08/08/91
WO-A1- 8603750	03/07/86	AU-B-	587010	03/08/89
		AU-D-	5308786	22/07/86
		CA-A-	1253806	09/05/89
		EP-A-B-	0205530	30/12/86
		JP-T-	62501706	09/07/87
		US-A-	4810488	07/03/89

For more details about this annex : see Official Journal of the European patent Office, No. 12/82

**This Page is Inserted by IFW Indexing and Scanning
Operations and is not part of the Official Record**

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☒ **BLACK BORDERS**
- ☐ **IMAGE CUT OFF AT TOP, BOTTOM OR SIDES**
- ☐ **FADED TEXT OR DRAWING**
- ☒ **BLURRED OR ILLEGIBLE TEXT OR DRAWING**
- ☐ **SKEWED/SLANTED IMAGES**
- ☐ **COLOR OR BLACK AND WHITE PHOTOGRAPHS**
- ☐ **GRAY SCALE DOCUMENTS**
- ☐ **LINE(S) OR MARK(S) ON ORIGINAL DOCUMENT**
- ☐ **REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY**
- ☐ **OTHER:** _____

IMAGES ARE BEST AVAILABLE COPY.

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.